DETAILED ACTION

Applicant's amendment and response received on 3/7/11 has been entered. Claims 1-2, 6, 8, 13, 16-17, 19, and 22-74 are now canceled. Claims 3-5, 7, 9-12, 14-15, 18, and 20-21 are currently pending and under examination. An action on the merits follows.

Those sections of Title 35, US code, not included in this action can be found in the previous office action.

Claim Rejections - 35 USC § 112

The rejection of claims 1-2, and 12-14 under 35 U.S.C. 112, second paragraph, for indefiniteness, is withdrawn in view of the cancellation of claims 1-2 and 13, and the amendment of claims 12 and 14 to depend on claim 3.

The rejection of claims 1-2, and 12-14 under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, is withdrawn in view of the cancellation of claims 1-2 and 13, and the amendment of claims 12 and 14 to depend on claim 3.

The rejection of claim 4 under 35 U.S.C. 112, second paragraph, for indefiniteness is withdrawn in view of the amendments to claim 4.

The rejection of claims 15-21 under 35 U.S.C. 112, second paragraph, for indefiniteness is withdrawn in view of the cancellation of claims 16-17 and 19, and further in view of the deletion of the word substantially from claims 15, 18, and 20-21.

Claims 9-10 are newly rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The applicant has amended the claims to depend on claim 3. There is no antecedent basis in either claims 9-10 or claim 3 for "said cancerous prostate cells". Thus, the metes and bounds of the claims cannot be determined.

Claim 14 is newly rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 14 has been amended to depend on claim 12, which now recites a prostate cancer stem cell. However, claim 14 refers to a prostate stem cell according to claim 12. Since claim 12 has been amended to recite a prostate cancer stem cell, there is no antecedent basis for "prostate stem cell" in claim 12. Thus, the metes and bounds of the claim cannot be determined.

Claim Rejections - 35 USC § 102

The rejection of claims 1-3, 5-7, 11-12, and 15 under 35 U.S.C. 102(b) as being anticipated by Collins et al. (2001), J. Cell Science, Vol. 114, 3865-3872, is withdrawn in view

of applicant's cancellation of claims 1-2, and 6, and applicant's amendment of claims 3, 5, 7, 11-12 and 15 to recite prostate cancer stem cells.

Claim Rejections - 35 USC § 103

The rejection of previously pending claims 8-10, 13-14, and 16-21 under 35 U.S.C. 103(a) as being unpatentable over Collins et al. (2001), J. Cell Science, Vol. 114, 3865-3872, in view of US Patent Application Publication 2007/0134794 (published 2007, with an effective filing date of 10/15/01), hereafter referred to as Mangano, is withdrawn over canceled claims 8, 13, 16-17, and 19, maintained over amended claims 9-10, 14, 18, and 20-21, and newly applied to amended claims 3-5, 7, 11-12, and 15. Thus, claims 3-5, 7, 9-12, 14-15, 18, and 20-21 are now included in this rejection. Applicant's amendments to the claims, arguments, and supporting evidence in the form of the post-filing Collins et al. reference published in 2005, have all been fully considered but have not been found persuasive in overcoming the rejection for reasons of record as discussed in detail below.

The applicant argues that the Collins et al. method is drawn to the isolation of prostate stem cells not prostate cancer stem cells and that further, the expression of CD133 is not an inherent property of stem cells isolated using the Collins et al. method, citing a later post-filing publication by Collins et al. published in 2005. In response, the rejection of record noted that that Collins et al. teaches a method for isolating prostate stem cells based on CD44 expression and adherence to collagen. The rejection of record cited Mangano et al. for the motivation to use the Collins method to isolate prostate cancer stem cells. The applicant has not provided any

arguments specific to the teachings provided by Mangano et al. except to say that Mangano et al. does not teach prostate cancer stem cells expressing CD133. However, as noted above and discussed in detail below, the expression of CD133 is considered an inherent property of the stem cell population isolated using the Collins et al. method.

Further, in regards to the expression of CD133 on prostate stem cells isolated using the Collins et al., the rejection of record stated that Collins et al. teaches a method for isolating an enriched population of prostate stem cells comprising 1) providing a cell preparation comprising prostate stem cells by digesting human prostate tissue with collagenase, and isolating basal epithelial cells within the stromal population through immunomagnetic positive selection of CD44 expressing cells, and 2) enrichment of prostate stem cells from the CD44 positive basal cell population through selection of cells which rapidly adhere to dishes coated with collagen type I (Collins et al., page 3866 and 3868). Collins et al. teaches that rapidly adhering CD44+ cells are further $\alpha 2\beta 1$ integrin bright, and are capable of differentiating into prostate glandular tissue including the generation of acini (Collins et al., page 3869). The rejection of record specifically pointed out that the method steps taught by Collins et al. include methods steps which are identical to those recited in independent claim 3. The rejection of record continued by stating that while Collins et al. does not test the rapidly adhering CD44+ $\alpha 2\beta 1$ integrin + prostate stem cells for the expression of the CD133 antigen or human epithelial antigen (also known in the art as Ep-CAM), the expression of CD133 antigen and human epithelial antigen by these prostate stem cells appears to be an inherent characteristic of prostate stem cells isolated using the Collins et al. method, which as noted above is the exact same method as recited in claim 3. Thus, contrary to applicant's arguments, the rejection does not state that CD44+ stem cells

inherently express CD133, the rejection of record stated that the selection of prostate stem cells based on CD44 expression and collagen adherence results in a cell population that inherently expresses CD133 and Ep-CAM. Nothing in the 2005 Collins et al. publication contradicts this finding. Figure 1a on page 10948 of Collins et al. (2005) shows results for colony forming efficiency of three different cell populations, including a CD44+/α2β1 hi/CD133+ and a CD44+/α2β1 hi/CD133- population. Note that the CD44+/α2β1 hi/CD133- population is referred to as a "transit amplifying population" on page 10947 of Collins et al. (2005). However, Collins et al. (2005) does not teach levels of CD133 expression that prostate stem cells selected for CD44 expression and collagen binding. Collins et al. teaches in the material and methods section that CD44+/α2β1 hi/CD133+ cells were isolated as previously described by Richardson et al. (2004) J. Cell Sci., Vol. 117, 3539-3545. Richardson et al., cited for the record as rebuttal evidence, in fact teaches that 1) the "transit amplifying population" is the non-rapidly adhering population, and thus different from the stem cell population isolated using the Collins et al. method, and that 2) the rapidly adhering population, which is +/α2β1 hi, contains cells expressing CD133 (Richardson et al., pages 3540, column 1, and page 3542). It is further noted that unlike the a CD44+/α2β1 hi/CD133+ population disclosed by Collins et al. (2005) which included positive selection of CD133, the instant methods simply recite the isolation of cells which adhere to collagen. Thus, is reiterated that a method of isolating prostate stem cells comprising selection of prostate basal cells for CD44+ expression and for rapid adherence to collagen as taught by Collins et al., and as recited in the instant methods, inherently comprises the isolation of prostate stem cells which express CD133. The claims recite no steps in addition

to those taught by Collins et al. Therefore, applicant's arguments concerning the teachings of Collins et al. are not found persuasive.

The applicant further argues that prostate cancer stem cells which are CD44+/α2β1 hi/CD133+ have enhanced colony forming activity as compared to cells which do not express CD133 and have a greater capacity to invade and form tumors in a xenograft model citing Figures 1b-c, and 2b from the instant specification and Figures 1A and 2B from Collins et al. (2005). However, the cell populations tested in the both the instant specification and in Collins et al. (2005) were isolated using positive selection for CD133 expression, a step not recited or required by the instant methods. As such, the cell population tested by the instant specification and Collins (2005) was isolated using a different method than that claimed. Therefore, in response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., increased proliferation/invasiveness etc.) are not recited in the rejected claim and further have not been demonstrated for the cell population isolated using the methods as claimed, which do not include a positive selection step for CD133 expression. Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

Therefore, it is maintained that based on the motivation provided by Mangano et al. to select and enrich for prostate stem cells or prostate cancer stem cells from source tissue which is a solid tumor or metastatic tissue, and the further teachings of Mangano et al. that cancer stem cells, including prostate cancer stem cells, share similar marker protein expression as the original stem cell, it would have been *prima facie* obvious to the skilled artisan at the time of filing to

practice the methods for selecting prostate stem cells taught by Collins et al. using primary prostate tumor tissue or metastatic prostate cancer tissue as the tissue source for isolating the stem cells, or alternatively it would have been *prima facie* obvious to the skilled artisan at the time of filing to select and enrich for prostate cancer stem cells using the methods for selecting prostate stem cells taught by Collins et al. The skilled artisan would further have had a reasonable expectation of success in isolating either prostate stem cells or prostate cancer stem cells from prostate tumor tissue or metastases using the Collins method of selecting for CD44+ cells, and further selecting for cells that rapidly adhere to collagen I (i.e. express high levels of $\alpha 2\beta 1$ integrin) since Mangano et al. teaches that both stem cells and cancer stem cells can be found in tumors and metastases, that cancer stem cells would be expected to express the same markers used for stem cell selection, and that stem cells versus cancer stem cells can be differentiated by their ability to form tumors in animals.

Finally, regarding the expression of AC133 antigen and human epithelial antigen on the cancer stem cells, while neither Collins et al. nor Mangano teach that prostate cancer stem cells express these markers, it is maintained that the expression of both AC133 and human epithelial antigen are considered to be an inherent characteristic of prostate cancer stem cells isolated using the Collins et al. method, which as noted above is the exact same method as recited in claim 3. The office does not have the facilities for examining and comparing applicant's product with the product of the prior art in order to establish that the product of the prior art does not possess the same material, structural and functional characteristics of the claimed product. In the absence of evidence to the contrary, the burden is upon the applicant to prove that the claimed products are functionally different than those taught by the prior art and to establish patentable differences.

See *Ex parte Phillips*, 28 USPQ 1302, 1303 (BPAI 1993), *In re Best*, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and *Ex parte Gray*, 10 USPQ2d 1922, 1923 (BPAI 1989).

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication from the examiner should be directed to Anne Marie S. Wehbé, Ph.D., whose telephone number is (571) 272-0737. If the examiner is not available, the examiner's supervisor, Joseph Woitach, can be reached at (571) 272-0739. For all official communications, the technology center fax number is (571) 273-8300. Please note that all official communications and responses sent by fax must be directed to the technology center

fax number. For informal, non-official communications only, the examiner's direct fax number is (571) 273-0737. For any inquiry of a general nature, please call (571) 272-0547.

The applicant can also consult the USPTO's Patent Application Information Retrieval system (PAIR) on the internet for patent application status and history information, and for electronic images of applications. For questions or problems related to PAIR, please call the USPTO Patent Electronic Business Center (Patent EBC) toll free at 1-866-217-9197. Representatives are available daily from 6am to midnight (EST). When calling please have your application serial number or patent number available. For all other customer support, please call the USPTO call center (UCC) at 1-800-786-9199.

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